MEMORANDUM

SUBJECT: **CHLORPROPHAM - REREGISTRATION CASE NO. 0271** - Toxicology Chapter for the Reregistration Eligibility Decesion Document on Chlorpropham

P.C. CODE: 018301 DP BARCODE NO.: D207525
TOX. CHEM. NO.: 510A SUBMISSION NO.: S466590
CAS NO.

FROM: William B. Greear, M.P.H.
Toxicology Branch II
Health Effects Division (7509C)

TO: Jess Rowland, Branch Chief
Risk Characterization and Analysis Branch
Health Effects Division (7509C)

THRU: Stephen C. Dapson, Ph.D., Branch Senior Scientist
Toxicology Branch II
Health Effects Division (7509C)

and

K. Clark Swentzel, Branch Chief
Toxicology Branch II
Health Effects Division (7509C)

CC: Betty Shackleford/Walter Waldrop, PM Team #53
Reregistration Branch
Special Review and Reregistration Division (7508W)

Attached please find the Toxicology Chapter for the Reregistration Eligibility Decesion Document on chlorpropham. This chapter is to be incorporated into the HED's RED for reregistration of chlorpropham.

B. Human Health Assessment

1. Toxicology Assessment

The toxicology data base in support of the food and non-food uses of chlorpropham is adequate and will support reregistration eligibility.

a. Acute Toxicity

Acute Toxicity

Test	Result	Category
Acute Oral LD_{50} (rat)[1]	> 4 g/kg	III
Acute Dermal LD_{50} (rabbit)[2]	> 5 g/kg	IV
Acute Inhalation LC_{50}	Requirement waived[3]	N/A
Eye Irritation (rabbit)[4]	Mild Irritant	III
Dermal Irritation (rabbit)[5]	Mild Irritant	IV
Skin Sensitization (guinea pig)[6]	Negative	N/A

[1] MRID 41013703, 41763601
[2] MRID 41013704
[3] The requirement for an acute inhalation study was waived by HED (memos dated 11/9/88 and 11/26/90). Chlorpropham technical cannot be prepared and tested in a respirable form.
[4] MRID 41013705, 41763301
[5] MRID 41013706, 41763501
[6] MRID 41013707, 41763401
N/A = not applicable

b. Subchronic Toxicity

A 21-day dermal study was conducted with male and female New Zealand white rabbits. Chlorpropham was applied to intact skin at dose levels of 0, 100, 500, or 1000 mg/kg/day for 6 hours/day, 7 days/week. On three occasions some animals were exposed for 24 hours. All dose levels produced dermal irritation consisting of erythema, edema, cracking, and scaling. Histopathological findings in the skin included minimal acanthosis, hyperkeratosis, and focal inflammatory cells. The only systemic effect was a dose-related increase in reticulocytes in blood of both sexes that was significant at the highest dose of 1000 mg/kg/day. Hematology revealed no other indications of anemia. An increase in spleen weight (relative to brain weight) at the high dose was possibly related to the increase in reticulocytes. The effect on reticulocyte count was consistent with hematological findings of erythrocyte destruction/loss in longer-term studies. The NOEL for dermal effects was less than the lowest dose of 100 mg/kg/day, and the LOEL was 100 mg/kg/day. The NOEL for systemic toxicity was 500 mg/kg/day, and the LOEL was 1000 mg/kg/day based on the increase in reticulocyte count. (MRID 41899901)

A 90-day feeding study with rats and a 28-day dog study were supplementary. The subchronic feeding study requirements are satisfied by the two-year rat and 60-week dog studies.

c. Chronic Toxicity/Carcinogenicity

In a two year toxicity/carcinogenicity study, chlorpropham (96% a.i.) was administered in the diet to groups of 50 male (104 weeks) and 50 female (101 weeks) Sprague-Dawley rats at dietary levels to provide an intake of 0, 30, 100, 500 or 1000 mg/kg/day. Additional animals (10/sex/group) received the same doses and were sacrificed at 53 weeks. At 100 mg/kg/day, red blood cell counts (RBC) were decreased about 10% in both sexes at weeks 26 and 53 and hemoglobin (HGB) and hematocrir (HCT) values were slightly but significantly reduced in females. At 12 months, a slight increase in splenic extra medullary hematopoiesis (erythropoiesis) and hemosiderosis was seen in feamles. Heomsiderosis was increased in severity and incidence at 24 months and marked cellularity in the bone marrow was observed, particularary in the females receiving 100 mg/kg/day, but the effects on the red cell parameters were not seen at 78 weeks or at termination. Serum cholesterol levels were slightly increased (40-50%a0 at weeks 53 and 78 in males receiving 100 mg/kg/day. In addition, in the two highest dose groups (500 and 100 mg/kg/day), there was an increase in the incidence and/or severity of hematopoiesis in the liver, spleen and bone marrow in both sexes; an increased incidence of hemosiderosis and congestion in the spleen in both sexes; and an increase pigment accumulation in the liver and the kidney tubules of both sexes. Also at the 500 and 1000 mg/kg/day dose levels in both sexes, there was a significant decrease in red blood cell parameters (RBC, HCT and HGB) and an increase in reticulocyte counts at most intervals of analysis as well as urinary bilirubin. A destruction of red blood cells and a compensatory response were clearly apparent in both sexes at $\geq$100 mg/kg/day. In addition, a decrease in body weight (20-30% lower than controls at 104 weeks; both sexes) and body weight gain (25-

40% lower than controls at 104 weeks; both sexes), an increase in food consumption, an increase in serun cholesterol, and an increase in spleen size and weight were also observed at 500 and 1000 mg/kg/day in both sexes. The LEL of 100 mg/kg/day is based on the effects on hematology parameters, hemosiderosis in the spleen, hematopoiesis in the spleen, erythropoiesis in the bone marrow, particularly in females, and increased serum chloesterol in males. The NOEL is 30 mg/kg/day. Under the conditions of the study, there was a significant increase in benign interstitial cell tumors in the testes of male trats receiving 1000 mg/kg/day (9/60 compared to 1/57 for controls).

Chlorpropham was fed in the diets of CD-1 mice for 18-months at dietary levels to provide a test material intake of about 0, 100, 500 or 1000 mg/kg/day.

NOEL (systemic) = 100 mg/kg/day.

LEL (systemic) = 500 mg/kg/day based on increased hemosiderosis of the spleen and increased hematopoiesis of the spleen, liver, and bone marrow in both sexes in response to destruction or loss of erythrocytes. Dark eyes and bluish extremities were also noted.

In addition, at the highest dose tested (limit dose of 100mg/kg/day) an increase in parent reticulocyte was seen in males at 12 and 18 months and in females at 12 months; this was accompanied by an increase in MCH and MCHC in both sexes. In addition, survival was significantly lower in males receiveing 100 mg/kg/day than in controls. High-dose males had increased speen and liver weight. The tset material was not found to be carcinogenic in this study.

On July 20, 1994, the HED Cancer Peer Review Committee classified chlorpropham in Group E (evidence of non-carcinogenicity for humans). The classification was supported by the following evidence: 1) a lack of carcinogenic potential demonstrated in mice and 2) the increase in benign Leydig cell tumors in rats occurred only at a dose in excess of a maximum tolerated dose.

e. Developmental Toxicity

Chlorpropham, technical (Lot# 237-2778 BR 21-80, about 98% pure), was administered daily by gavage (corn oil vehicle) to 25 presumed pregnant Sprague Dawley rats per group at 0, 100, 350 or 1000 mg/kg/day from day 6 through 19 of gestation (MRID 00093921). From gestational day 6 to 20 maternal body weight gain was 89% of controls, $p \leq 0.05$, at 350 mg/kg-rat and 83% of controls, $p \leq 0.01$, at 1000 mg/kg-rat. Spleen weights increased 157% of controls at 350 mg/kg-rat and 171% of controls at 1000 mg/kg/day. Possible developmental toxicity was noted at the 1000 mg/kg-rat dose level by an increase in the 14th rudimentary rib (52% vs. 24% in control litters). Historical control data indicated that in the strain of rat, the incidence of 14th rudimentary rib ranged from 8% to 42.9% in litters. The maternal toxic LOEL = 350 mg/kg/day and the NOEL = 100 mg/kg/day based

on body weight gain decrement. The developmental toxic LOAEL = 1000 mg/kg/day and the NOAEL = 350 mg/kg/day based on increased incidence of 14th rudimentary rib. This study is classified Core-Minimum Data (Acceptable) and satisfies the requirement (83-3) for a developmental toxicity (teratology) study in rats.

In a developmental toxicity study (MRID 00129939), pregnant female Sprague-Dawley COBS CD rats were given multiple daily doses of 40.2% chlorpropham on Hi-Sil 233 by intragastric intubation at dose levels of 0, 0, 40, 400 and 2000 mg/kg/day CIPC. They were dosed during organogenesis (gestation days 6-19) and sacrificed on gestation day 20. Lethality of dams was observed at 2000 mg/kg/day (3 of 25 died between days 10 and 13). Decreased body weight gain, pale extremities and ears, bloodied facial fur and stained urogenital fur were observed at 2000 mg/kg/day. Pale extremities and ears were also observed at 400 mg/kg/day. Cerebral hemorrhage, darkening and enlargement of the spleen (possibly stressed induced hematopoiesis) and reversible gastrointestinal bleeding and lesion were observed at necropsy in 2000 mg/kg/day dams. Enlarged darkened spleens were also observed at 400 mg/kg/day. A high rate of post-implantation loss due to early resorption was observed at 2000 mg/kg/day. Fetal weights were 20% lower at 2000 mg/kg/day compared to controls and other dosed animals. Skeletal anomalies observed at 2000 mg/kg/day included bent ribs and limb bones, maligned sternebrae, and reduced ossification of the pubic bones and vertebral arches. The LOAEL for maternal toxicity was 400 mg/kg/day based on pale extremities and ears and enlarged darkened spleens. The NOAEL was 40 mg/kg/day. The LOAEL for developmental effects was 2000 mg/kg/day based on skeletal anomalies and increased early resorption. The NOAEL was 400 mg/kg/day.
The study is classified as Guideline and it satisfies the requirement for a guideline series 83-3a developmental toxicity study.

Chlorpropham, technical (98.5% pure), was administered daily by gavage (Vehicle was 1% methylcellulose in water) to 16 presumed pregnant New Zealand White rabbits per group at 0, 125, 250 or 500 mg/kg/day from day 6 through 18 of gestation MRID 00129940). An increased incidence in the number of animals and number of clinical observations such as cold ears, soiled ano-genital area/blood in urine and reduced fecal output was noted at 500 mg/kg/day. Body weights and body weight gains were comparable with controls in all groups. In a range-finding study at 0, 200, 500, 1500 and 800 mg/kg/day all animals at 1500 and 800 mg/kg/day were killed in a moribund condition. Thus, 500 mg/kg/day was adequate (sufficiently close to a toxic dose level) to determine potential developmental toxicity from chlorpropham exposure. Possible developmental toxicity was noted at the 500 mg/kg-rabbit dose level by an increased resorption and increased post implantation loss. The submitted early and late resorption combined was statistically significant increased (1.8/litter versus 0.7/litter in controls, $p \leq 0.01$) at 500 mg/kg/day and post implantation loss was statistically significantly increased (19.0% versus 7.2% in controls, $p \leq 0.05$) at 500 mg/kg/day. Both of these were higher than the respective mean, but within the historical control range submitted with the study. Early and late embryonic death mean of 1.0/litter, range of 0.0-2.5/litter and post implantation loss mean of 10.8%, range of 0.0-24.7%. The maternal toxic LOAEL = 500 mg/kg/day and the NOAEL = 250 mg/kg/day based on clinical signs of cold ears and

reduced fecal output. The developmental toxic LOAEL = 500 mg/kg/day and the NOAEL = 250 mg/kg/day based on increased resorption and post implantation loss. This study is classified as Core Minimum Data (Acceptable) and satisfies the requirement (§ 83-3) for a developmental toxicity (teratology) study in rabbits.

f. Reproduction

In a reproductive toxicity study (MRID 00129545), chlorpropham (98%) was administered in the diet at 0, 1000, 3000 or 10,000 ppm (approximate doses of 0, 50, 150 or 500 mg/kg/day) to male and female Sprague-Dawley rats (15 male, 30 female per group) for 14 weeks prior to dosing and during the mating, gestation and lactation periods (total of 164-165 days). Mating and fertility indices in the F_0 and F_1 rats were not significantly reduced. Similarly, there was no effect on the length of gestation, mean litter size and survival for the F_1 and F_2 pups. There were no compound related abnormalities. Body weight gain was slowed in rats dosed at 3000 and 10,000 ppm, but no effect was seen at 1000 ppm. No compound related gross lesions were seen in any rats, except the culled F_1 adults. They included dose-related histopathologic findings of brown pigment granules in the reticuloendothelial cells of the spleen and liver and the convoluted tubular epithelial cells of the kidney, and marrow hypercellularity. Rats dosed at 3000 and 10,000 ppm were most affected. Organ weight changes in the F_1 pups (lactation day 21) included mild dose-related decreases in absolute and relative ovary weights in all dosed groups and mild decreases in absolute and organ/brain weight ratios for liver (3000 and 10,000 ppm) and spleen (10,000 ppm). In the F_1 adults, a severe increase in absolute and relative spleen weights was seen in males (10,000 ppm) and females (3000 and 10,000 ppm). The F_2 pups had mild to moderate absolute and relative organ weight decreases for ovaries (3000 and 10,000 ppm) and spleens (10,000 ppm). Measurements of cholinesterase levels in the brain, plasma and erythrocytes of the F_1 rats did not reveal any significant changes. The only compound related effect seen in the 1000 ppm dose group was a mild decrease in mean ovary weights in the F_1 pups. Since no ovarian lesions were observed grossly or microscopically in these pups and the F_1 adults had normal ovarian morphology, the decreased ovarian weights were probably just an indication of slight development delay. The LOAEL for reproductive effects was not determined; the NOAEL $\geq$ 10,000 ppm 500 mg/kg/day). The LOAEL for systemic effects was 3000 ppm (150 mg/kg/day) based on slow weight gain; microscopic lesion in the kidneys, spleen, liver and marrow; gross splenic lesions; organ weight changes in the ovaries, liver and spleen. The systemic NOAEL = 1000 ppm (50 mg/kg/day). The study is classified as Core-Guideline and it satisfies the requirement for a guideline series 83-4 reproductive toxicity study.

g. Mutagenicity

Three acceptable studies on chlorpropham were available for review; summaries of these studies follow:

Gene Mutations

1) Mouse lymphoma (L5178Y TK +/-)(MRID 00129938) - Complete toxicity occurred at chlorpropham concentrations of 1000-10,0000 μg/ml with or without metabolic activation (PCB-induced rat liver S9). Concentrations of 13 to 75 μg/ml were tested without metabolic activation; growth was 41 to 100% of control cultures. Concentrations of 13 to 100 μg/ml were tested with metabolic activation; growth was 8 to 52% of control cultures. Chlorpropham had no effect on mutation frequency with or without metabolic activation.

Chromosome Aberrations

2) In vitro chromosome aberrations in CHO cells (MRID 41846201) -Metaphase cells were collected 10 and 20 hours after treatment. Concentrations of 149 μg/ml and higher were toxic. Concentrations tested ranged from 10 to 160 μg/ml with or without metabolic activation (PCB-induced rat liver S9). Chlorpropham was positive with metabolic activation at moderately toxic doses (120 and 140 μg/ml). Chlorpropham was negative without metabolic activation, but this portion was incompletely performed.

Other Mutagenic Mechanisms

3) In vitro cell transformation using Syrian hamster embryo cells (MRID 41845501) - Six concentrations of chlorpropham (5-30 μg/ml) were tested in a continuous (7-day) exposure regimen. Five concentrations (85-115 μg/ml) were tested for 24 hours, which included a 7-day refeeding regimen. Chlorpropham was positive for producing morphological transformations. Both the continuous exposure and the 24 hour exposure resulted in a significant increase in the frequency of transformations.

Other Metabolites

4) Two potential metabolites of chlorpropham were evaluated in the Salmonella typhimurium mutation assay using tester strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538. The compounds tested were isopropyl 5-chloro-2-hydroxycarbanilate and isopropyl 3-chloro-4-hydroxycarbanilate. Both tested negative with and without metabolic activation (PCB-induced rat liver S9) (MRID 00126733, 00126734).

h. Metabolism

The pharmacokinetics of chlorpropham was evaluated in male and female Sprague-Dawley rats following a single intravenous dose (0.5 mg/kg), single oral low dose (5 mg/kg), single oral high dose (200 mg/kg), or repeated oral low doses (5 mg/kg/day for 15 days). With all dosing regimens, chlorpropham was rapidly absorbed and essentially completely metabolized prior to excretion in urine with small amounts in feces. Within 24 hours 82-92% of the radiolabel was recovered in the urine and 3-5 % in the feces. Peak excretion at the low dose occurred at 4-12 hours (49-62% of the dose) and at the high dose between 8-24 hours (59-64% of the dose). Less than 0.3% of doses were recovered at C^{14}-CO_2 over a three day

period. The approximate half-life of chlorpropham was 8 hours at the low dose and 9 hours at the high dose in males and females. Three major metabolic routes were proposed: (1) hydroxylation at the 4'-position and conjugation, (2) oxidation of the isopropyl side chain to form isopropanol and isopropinate moieties; (3) decarbamilation to form 3-chloroaniline followed by N-acetylation, 4'-hydroxylation, and conjugation. (MRID 42006901)

i. Neurotoxicity

In an acute oral delayed neurotoxicity study (MRID 00093915), groups of 10 domestic hens were dosed with 0 (corn oil control), 1250, 2500 or 5000 mg/kg/day chlorpropham. Ten hens were dosed with 500 mg/kg TOCP as the positive control. No deaths occurred and all hens appeared to be in good health. All TOCP treated hens showed signs of ataxia and one hen was sacrificed on day 15. All control and chlorpropham treated hens showed an increase in body weight in the post-dosing period (21 days). The TOCP treated hens showed a decrease in body weight. Food consumption was variable in all groups. There were no signs of delayed neurotoxicity (ataxia) in chlorpropham treated hens. Histologic lesions were observed in the TOCP treated hens which correlated with the ataxia observed. There were no histologic lesions considered to be treatment related in chlorpropham treated hens. The study is classified as Core-Minimum Data and it satisfies the requirement for a guideline series 81-7 acute delayed toxicity study.

j. Endpoints to be used for Risk Assessment

1a) Acute Reference Dose (Acute RfD) Females (13 + years)

Study Selected: Developmental Toxicity - Rabbit §83-3b

MRID No.: 00129940

Executive Summary: Chlorpropham, technical (98.5% pure), was administered daily by gavage (Vehicle was 1% methylcellulose in water) to 16 presumed pregnant New Zealand White rabbits per group at 0, 125, 250 or 500 mg/kg/day from day 6 through 18 of gestation. An increased incidence in the number of animals and number of clinical observations such as cold ears, soiled ano-genital area/blood in urine and reduced fecal output was noted at 500 mg/kg/day. Body weights and body weight gains were comparable with controls in all groups. In a range-finding study at 0, 200, 500, 1500 and 800 mg/kg/day all animals at 1500 and 800 mg/kg/day were killed in a moribund condition. Thus, 500 mg/kg/day was adequate (sufficiently close to a toxic dose level) to determine potential developmental toxicity from chlorpropham exposure. Possible developmental toxicity was noted at the 500 mg/kg-rabbit dose level by an increase in resorption and increased post implantation loss. The submitted early and late resorption combined was statistically significant increased (1.8/litter versus 0.7/litter in controls, $p \leq 0.01$) at 500 mg/kg/day and post implantation loss was statistically significantly increased (19.0% versus 7.2% in controls, $p \leq 0.05$) at 500 mg/kg/day. Both of these were higher than the respective mean, but within the historical control range submitted with the study. Early and late embryonic death mean of 1.0/litter, range of 0.0-2.5/litter and post implantation loss mean of 10.8%, range of 0.0-24.7%. clinical signs of cold ears and reduced fecal output. The developmental

toxic LOAEL = 500 mg/kg/day and the NOAEL = 250 mg/kg/day based on increased resorption and post implantation loss.

This study is classified as Core Minimum Data (Acceptable) and satisfies the requirement (§ 83-3) for a developmental toxicity (teratology) study in rabbits. This repeat DER is review of the same study reviewed on 1/10/83 (HED Doc.# 004209).

Dose and Endpoint for Risk Assessment: Developmantal NOAEL based on increased resorption and post implantation loss at 500 mg/kg/day (LOAEL).

Comments about Study/Endpoint: The developmental effects are presumed to occur after a single expsoure (dose). Since this in an *in utero* effect, it is applicable only to the population subgroup Females 13+.

Uncertainty Factor (UF): 100 (includes 10x for intra-species extrapolation and 10x for inter-species variation).

$$\textbf{Acute RfD} = \frac{\text{250 mg/kg/day NOAEL)}}{\text{100 (UF)}} = \textbf{2.5 mg/kg/day}$$

This risk assessment is required.

1b) Acute Reference Dose (Acute RfD) General Population including Infants and Children.

An appropriate endpoint attributable to a single exposure was not available from the toxicity studies, including the developmental toxicity studies; the maternal toxicity in these studies are not attributable to a single exposure. Therefore, there is no dose selected for the general population including infants and children

This risk assessment is NOT required for this population (No acute RfD)

2) Chronic RfD

The RfD was established in 1994 by the RfD Committee.

Study Selected: Chronic Feeding - Dog §83-1

MRID No.: 42189501

Executive Summary: A 60-week study was conducted with male and female beagle dogs. Chlorpropham was fed in the diet to give dose levels of 0, 5, 50, 350 or 500 mg/kg/day. The diets containing 350 or 500 mg/kg/day were unpalatable causing marked reductions in food consumption and body weight gain during the initial weeks of the study. Food consumption returned to normal by the dogs adapting to the diet or manipulation of the test material concentration; however, bodyweight gain of the 350 and 500 mg/kg/day dose groups remained depressed throughout the study. Anemia was evident at the two highest dose levels. Erythrocyte count, hemoglobin and hematocrit

were reduced, and mean corpuscular volume (MCV) was increased. Changes in thyroid function and morphology were prominent effects of treatment. At 50 mg/kg/day and above thyroid weight was increased and histopathological changes were observed. The thyroid showed moderate to marked changes characterized by irregular shaped follicles lined by medium to high cuboidal epithelium; follicles contained clear to pale stained colloid. Serum T_3 and T_4 levels were reduced at 350 and 500 mg/kg/day. Thyroid response to TSH was depressed at these dose levels. Cholesterol was increased at 350 and 500 mg/kg/day. The NOAEL was 5 mg/kg/day. The LOAEL was 50 mg/kg/day based on evidence of thyroid effects at this dose level. (MRID 42189501)

Dose and Endpoint for Establishing RfD: NOAEL = 5 mg/kg/day based on thyroid effects at 50 mg/kg/day (LOAEL).

Uncertainty Factor(s): 100 (includes 10x for intra-species extrapolation and 10x for inter-species variation).

$$\textbf{Chronic RfD} = \frac{\text{5 mg/kg/day (NOAEL)}}{\text{100 (UF)}} = \textbf{0.05 mg/kg/day}$$

Comments about Study/Endpoint/Uncertainty Factor(s): The HIARC concurred with the dose, endpoint, uncertainty factor, and the study used in 1994 by the RfD/Peer Review Committee.

This risk assessment is required.

3) Occupational/Residential Exposure

a) Dermal Absorption

Dermal Absorption Factor: No dermal absorption studies are available. The Committee estimated a dermal absorption rate of 50% based on the results of an oral developmental toxicity and a 21-day dermal toxicity study in the same species (rabbits) with similar endpoints (i.e. alterations in hematopoietic system).

In the oral developmental toxicity study in rabbits, the maternal NOAEL was 500 mg/kg/day and the LOAEL was 500 mg/kg/day based on clinical signs of cold ears which are attributable to anemia (MRID 00129940).

In the 21-day dermal toxicity study in rabbits, the systemic toxicity NOAEL was 500 mg/kg/day and the LOAEL was 1000 mg/kg/day based on increased reticulocyte count which may be indicative of a decreased red cell life span and subsequent increase in hemopoiesis (MRID 41899901).

A ratio of the LOAELs from the oral and dermal studies, indicated an approximate dermal absorption rate of 50% (oral LOAEL 500 mg/kg/day / dermal LOAEL of 1000 mg/kg/day x 100 = 50%).

Dermal Absorption Factor: 50% (estimated)

b) Short-Term Dermal (1-7 days)

Study Selected: 21-day Dermal Toxicity Study - Rat §82-2

MRID No.: 41899901

Executive Summary: Groups of male and female New Zealand White rabbits received repeated dermal applications of Chlorproham (96.2%) at dose levels of 0, 100, 500 or 1000 mg/kg/day, 6 hours/day for 21 consecutive days. Dermal irritation consisted of minimal to slight acanthosis, hyperkeratosis, and focal inflammatory infiltrate of the treated skin. There were no treatment-related effects on survival, body weight, organ weight or clinical chemistry. Systemic toxicity was characterized as increases in reticulocyte count (208% and 233% of controls in males and females, respectively $p < 0.01$). The NOAEL was 500 mg/kg/day and the LOAEL was 1000 mg/kg/day based on the increase in reticulocyte counts.

Dose and Endpoint for Risk Assessment: Systemic toxicity = 500 mg/kg/day based on the increase in reticulocyte counts at 1000 mg/kg/day (LOAEL).

Comments about Study/Endpoint:Study Selected: The NOAEL (500 mg/kg/day) in this study is comparable to the dermal equivalent dose derived by using the developmental NOAEL of 250 mg/kg/day established in the developmental rabbit study and the use of a 50% dermal absorption rate ($250 \div 0.5 = 500$ mg/kg/day).

This risk assessment is required.

c) Intermediate-Term Dermal (7 Days to Several Months)

Study Selected: Chronic Feeding - dog §83-1

MRID No.: 42189501

Executive Summary: see Chronic RfD in section II. B.

Dose and Endpoint for Risk Assessment: NOAEL = 5 mg/kg/day based on thyroid effects at 50 mg/kg/day (LOAEL).

Comments about Study/Endpoint: The endpoint selected for this risk assessment is based on the statistically significant decreases in thyroxine (T_4) levels seen at Week 14 in male at 50, 350 or 500 mg/kg/day. T_4 levels were also decreased

at this interval but the decreases did not show statistical significance when compared to controls. Additionally, this endpoint is supported by the results of a 28-day feeding study in rats , in which the LOAEL of 50 mg/kg/day was established based on histopathological alterations in the thyroid glands; the NOAEL was 5 mg/kg/day (MRID 41899001). Since an oral NOAEL was selected a dermal absorption rate of 50% should be used for route-to-route extrapolation.

This risk assessment is required.

d) Long-Term Dermal (Several Months to Life-Time)

Study Selected: Chronic Feeding - dog §83-1

Executive Summary: see Chronic RfD in section II. B.

Dose and Endpoint for Risk Assessment:NOAEL = 5 mg/kg/day based on thyroid effects at 50 mg/kg/day (LOAEL).

Comments about Study/Endpoint: This dose/endpoint/study was selected to derived the RfD. Since an oral NOAEL was selected a dermal absorption rate of 50% should be used for route-to-route extrapoaltion.

e) Inhalation Exposure (Any Time Period)

The Committee selected the oral NOEL of 5 mg/kg/day for inhalation risk assessments for any time period (short, intermediate, or long-term) due to the lack of an inhalation study (study was waived) and because of the concern for potential for exposure via this route from both occupational and residential exposures.

Since the dose identified for inhalation risk assessment is from an oral study (i.e., an oral NOEL was selected), the following steps should be used for route-to-route extrapolation:

Step 1 The inhalation exposure component (i.e. ug a.i/L./day) using 100% absorption rate (default value) and application rate should be converted to an **equivalent oral dose** (mg/kg/day).

Step 2 The Intermediate and Long-Term dermal expsoure component (mg/kg/day) using 50% absorption rate and application rate should be converted to an **equivalent oral dose** (mg/kg/day). Combine this dose to the converted dose in Step 1.

Step 3 This combined dose should then be compared to the oral NOAEL of 5 mg/kg/day to calculate the MOEs.

NOTE: For Short-Term risk assessment, the dermal exposure should NOT be combined with inhalation expsoure since a dermal NOAEL was used. However, it is appropriate to combine the dermal and inhalation exposure to get the total exposure for Intermediate and Long-Term risk assessments since oral NOAEL was selected for these exposures.

Separate MOEs should be calculated for Short-Term dermal (using the Dermal NOAEL) and Short-Term inhalation exposures.

4) Recommendation for Aggregate Exposure Risk Assessments

For **acute** aggregate exposure risk assessment, combine the high end exposure values from food + water and compare it to the acute RfD.

Aggregate risk assessments for short, intermediate or long-term exposure from dermal and inhalation exposures can NOT be performed since different toxicology endpoints were identified for the oral (developmental toxicity), dermal (hematopoietic), and inhalation (thyroid effects) exposure risk assessments.

5) Margins of Exposures for Occupational/Residential Exposure Risk Assessments

A MOE of 100 is adequate for occupational exposure risk assessments. The MOE for residential exposure will be determined during risk characterization by the FQPA Safety Committee.

k. World Health Organization (WHO) Review

Chlorpropham was evaluated at the Joint FAO/WHO Meeting on Pesticide Residues in 1963 and 1965, but no Acceptable Daily Intake (ADI) was allocated.

l. Dose Response Assessment

1) Determination of Susceptibility

The Hazard Identification Assessment Review Committee (HIARC) determined that the available Agency Guideline studies indicated no increased susceptibility of rats or rabbits (quantitatively or qualitatively) to *in utero* and/or pre/postnatal exposure to chlorpropham. In the two prenatal developmental toxicity studies in rats, the NOAELs for developmental toxicity were higher than those for maternal toxicity. In the developmental toxicity study in rabbits, developmental toxicity was seen only in the presence of maternal toxicity at the highest dose tested. In the two-generation reproduction study in rats, no offspring toxicity was observed even at the highest dose tested (see Attachment 1).

The Committee recommended that the 10X FQPA safety factor be removed since: 1) the toxicology data base is complete; 2) there is no indication of increased susceptibility of rats or rabbit fetuses to *in utero* and/or postnatal exposure in the developmental and reproductive toxicity studies; 3) a developmental neurotoxicity study is not required; 4) dietary (food) exposure estimates are partially refined (using reassessed tolerances, % CT, and interim tolerances for milk and meat) resulting in a more realistic estimate of dietary exposure; 5) quantifiable contamination of surface or ground water is not likely to result from this use; and 6) there are currently no registered residential uses of chlorpropham, therefore, this type of exposure to infants and children is not expected.

BIBLIOGRAPHY

Guideline	MRID	Citation
81-1	41013703	Dougherty, K. (1989) The Acute Oral Toxicity of Chlorpropham Technical (SX-1817) in Adult Male and Female Rats: Project ID: CEHC 2993; S-3173. Unpublished study prepared by Chevron Environmental Health Center, Inc. 36 p.
81-1	41763601	Krohmer, R. (1990) Acute Oral Toxicity Evaluation of Chlorpropham in Rats: Lab Project Number: 393A-101-010-89. Unpublished study prepared by T.P.S., Inc. 39 p.
81-2	41013704	Dougherty, K. (1989) The Acute Dermal Toxicity of Chlorpropham Technical (SX-1817) in Adult Male and Female Rabbits: Project ID: CEHC 2994; S-3174. Unpublished study prepared by Chevron Environmental Health Center, Inc. 14 p.
81-4	41013705	Dougherty, K. (1989) The Acute Eye Irritation Potential of Chlorpropham Technical (SX-1817) in Adult Albino Rabbits: Project ID: CEHC 2995; S-3175. Unpublished study prepared by Chevron Environmental Health Center. 16 p.
81-4	41763301	Krohmer, R. (1990) Primary Ocular Irritation Evaluation of Chlorpropham in Rabbits: Lab Project Number: 393E-303-912-89. Unpublished study prepared by T.P.S., Inc. 28 p.
81-5	41013706	Dougherty, K. (1989) The Four-Hour Skin Irritation Potential of Chlorpropham Technical (SX-1817) in Adult Albino Rabbits: Project ID: CEHC 2996; S-3176. Unpublished study prepared by Chevron Environmental Health Center, Inc. 17 p.
81-5	41763501	Krohmer, R. (1990) Primary Dermal Irritation Evaluation of Chlorpropham in Rabbits: Lab Project Number: 393D -302-211-89. Unpublished study prepared by T.P.S., Inc. 27 p.
81-6	41013707	Dougherty, K. (1989) Modified Buehler Test for the Skin Sensitization Potential of Chlorpropham Technical: Project ID: CEHC 2997; S-3177. Unpublished study prepared by Chevron Environmental Health Center, Inc. 47 p.

81-6	41763401	Krohmer, R. (1990) Dermal Sensitization Potential of Chlorpropham in Guinea Pigs: Lab Project No.: 393B-201-215-89. Unpublished study prepared by T.P.S., Inc. 41 p.
81-7	00093915	Ross, D.B.; Roberts, N.L.; Phillips, C.N.K.; et al. (1980) The Acute Oral Toxicity (LD_{50}) and the Neurotoxic Effects of CIPC on the Domestic Hen: PPG 4 NT/80188. (Unpublished study received Jan 25, 1982 under 748-161; prepared by Huntingdon Research Centre, England, submitted by PPG Industries, Inc., Barberton, Ohio; CDL:246648-A)
82-2	41899901	Krohmer, R. (1990) 21 Day Dermal Toxicity Evaluation of Chlorpropham in Rabbits: Lab Project Number: 393F-304-231-89. Unpublished Study prepared by T.P.S., Inc. 168 p.
83-1b	42189501	Wedig, J. (1992) One Year Chronic Study of Chlorpropham in Dogs: Lab Project Number: 393J-502-640-89. Unpublished study prepared by T.P.S., Inc. 897 p.
83-1a, 83-2a	42754701	Botta, J. (1993) 24 Month Combined Oncogenicity/Toxicity Evaluation of Chlorpropham in Rats: Final Report: Lab Project Number: 393L-103-055-89. Unpublished study prepared by T.P.S., Inc. 3327 p.
83-2b	42530301	Botta, J. (1992) 18 Month Oncogenicity Evaluation of Chlorpropham in the Mouse: Lab Project Number: 393K-002-050-89. Unpublished study prepared by T.P.S., Inc. 1873 p.

83-3a	00093921	Rodwell, D.E.; Krabbe, R.; Werchowski, K.M. (1981) A Teratology Study in Rats with CIPC: WIL-81107. (Unpublished study received Jan 25, 1982 under 748-161; prepared by WIL Research Laboratories, Inc., submitted by PPG Industries, Inc., Barberton, Ohio; CDL:246650-A)
83-3b	00129940	James, P.; Billington, R.; Clark, R.; et al. (1983) A study of the Effect of CIPC on Pregnancy of the Rabbit: HRC Report No. PPG 5&7/8328. (Unpublished study received Jul 26, 1983 under 748-161; prepared by Huntingdon Research Centre, Eng., submitted by PPG Industries, Inc., Barberton, OH; CDL:250809-C)
83-4	00129545	Schroeder, R.; Daly, I.; Hogan, G.; et al. (1983) A Two Generation Reproduction Study in Rats with CIPC: Project No. 81-2573. Final rept. (Unpublished study received Jul 19, 1983 under 748-161; prepared by Bio/dynamics, Inc., submitted by PPG Industries, Inc., Barberton, OH; CDL:250764-A; 250765; 250766)
84-2	00129938	Kirby, P.; Pizzarello, R.; Rogers, A.; et al. (1983) L5178Y/TK± Mouse Lymphoma Mutagenesis Assay: … Test Article CIPC, Isopropyl 3-Chlorocarbanilate: Study No. T1890.701. (Unpublished study received Jul 26, 1983 under 748-161; prepared by Microbiological Assoc., submitted by PPG Industries, Inc., Barberton, OH; CDL:250808-A)
84-2	41846701	Murli, H. (1991) Mutagenicity Test on Chlorpropham in an In Vitro Cytogenetic Assay Measuring Chromosomal Aberration Frequencies in Chinese Hamster Ovary (CHO) Cells: Final Report: Lab Project No: 12276-0-437. Unpublished study prepared by Hazleton Laboratories America, Inc. 60 p.
84-2	41845501	Poiley, J. (1991) In Vitro Transformation Assay of Chlorpropham Using Syrian Hamster Cells: Lab Project Number: HLA A2276-0-485R. Unpublished study prepared by Hazleton Labs America, Inc. 87 p.
84-2	00126733	Haworth, S.; Lawlor, T.; Burke, J.; et al. (1983) Salmonella/Mammalian-microsome Plate Incorporation Mutagenicity Assay (Ames Test): PPG-134: Study No. T1888.501. (Unpublished study received Apr 11, 1983 under 748-233; prepared by Microbiological Assoc.,

		submitted by PPG Industries, Inc., Barberton, OH; CDL: 249883-A)
84-2	00126734	Haworth, S.; Lawlor, T.; Burke, J; et al. (1983) Salmonella/Mammalian-microsome Plate Incorporation Mutagenicity Assay (Ames Test): PPG-154: Study No. T1889.501. (Unpublished study received Apr 11, 1983 under 748-233; prepared by Microbiological Assoc., submitted by PPG Industries, Inc., Barberton, OH; CDL: 249883-B)
85-1	42006901	Robinson, R.; Liu, D. (1991) Metabolism of 14-Carbon Chlorpropham in Rats: Definitive FIFRA Study, Metabolism Analysis and Quantitation: Final Report: Lab Project Number: XBL90051: RPT0058. Unpublished study prepared by Xenobiotic Labs, Inc. and Biological Test Center. 615p.

HED Doc. No. 012911 - **ATTACHMENT #1**

DATE: October 16, 1998

MEMORANDUM

SUBJECT: ***CHLORPROPHAM*** - Report of the Hazard Identification Assessment Review Committee

FROM: William B. Greear
Toxicology Branch II
Health Effects Division (7509C)

and

Jess Rowland, Executive Secretary
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

THROUGH: K. Clark Swentzel, Chairman
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Jess Rowland, Chief
Risk Characterization and Analysis Branch
Health Effects Division (7509C)

PC Code: 018301

On September 15, 1998, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology data base on chlorpropham, re-assessed the toxicological endpoints for acute dietary as well as occupational/residential exposure risk assessments. The HIARC also addressed the potential enhanced sensitivity of infants and children from exposure to chlorpropham as required by the Food Quality Protection Act of 1996. The Committee's conclusions are presented in this report.

Committee Members in Attendance

Members present were Karl Baetcke, Robert Fricke, John Redden, Jess Rowland (Executive Secretary), Clark Swentzel (Chairman), William Burnam, Karen Hamernick and Sanjivani Diwan. Members in absentia: Melba Morrow, Mike Metzger and Nancy McCarrol.

Other HED members present: Brenda Tarplee, Roger Hawks, Elizabeth Mendez, Ray Kent, Pat Gaunt, and Stephen Dapson.

Data Presentation and Report Preparation: _____
William B. Greear, M.P.H., D.A.B.T.
Toxicologist

Report Concurrence: _____
Jess Rowland
Executive Secretary

I. INTRODUCTION

On September 15, 1998, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology data base of chlorpropham and selected doses and endpoints for acute dietary, as well as occupational and residential exposure risk assessments, and addressed the sensitivity of infants and children from exposure to chlorpropham as required by the Food Quality Protection Act (FQPA) of 1996. The application of the 10x factor for potential enhanced sensitivity of infants and children from exposure to chlorpropham will be determined by the FQPA Safety Factor Committee (FQPA SFC). The HIARC's conclusions are presented below.

II. HAZARD IDENTIFICATION

A1. Acute Reference Dose (Acute RfD) **Females (13 + years)**

Study Selected:	Developmental Toxicity - Rabbit	§83-3b
MRID No.:	00129940	

Executive Summary: Chlorpropham, technical (98.5% pure), was administered daily by gavage (Vehicle was 1% methylcellulose in water) to 16 presumed pregnant New Zealand White rabbits per group at 0, 125, 250 or 500 mg/kg/day from day 6 through 18 of gestation. An increased incidence in the number of animals and number of clinical observations such as cold ears, soiled ano-genital area/blood in urine and reduced fecal output was noted at 500 mg/kg/day. Body weights and body weight gains were comparable with controls in all groups. In a range-finding study at 0, 200, 500, 1500 and 800 mg/kg/day all animals at 1500 and 800 mg/kg/day were killed in a moribund condition. Thus, 500 mg/kg/day was adequate (sufficiently close to a toxic dose level) to determine potential developmental toxicity from chlorpropham exposure. Possible developmental toxicity was noted at the 500 mg/kg-rabbit dose level by an increase in resorption and increased post implantation loss. The submitted early and late resorption combined was statistically significant increased (1.8/litter versus 0.7/litter in controls, $p \leq 0.01$) at 500 mg/kg/day and post implantation loss was statistically significantly increased (19.0% versus 7.2% in controls, $p \leq 0.05$) at 500 mg/kg/day. Both of these were higher than the respective mean, but within the historical control range submitted with the study. Early and late embryonic death mean of 1.0/litter, range of 0.0-2.5/litter and post implantation loss mean of 10.8%, range of 0.0-24.7%. clinical signs of cold ears and reduced fecal output. The developmental toxic LOAEL = 500 mg/kg/day and the NOAEL = 250 mg/kg/day based on increased resorption and post implantation loss.

This study is classified as Core Minimum Data (Acceptable) and satisfies the requirement (§ 83-3) for a developmental toxicity (teratology) study in rabbits. This repeat DER is review of the same study reviewed on 1/10/83 (HED Doc.# 004209).

Dose and Endpoint for Risk Assessment: Developmantal NOAEL based on increased resorption and post implantation loss at 500 mg/kg/day (LOAEL).

Comments about Study/Endpoint: The developmental effects are presumed to occur after a single expsoure (dose). Since this in an *in utero* effect, it is applicable only to the population subgroup Females 13+.

Uncertainty Factor (UF): 100 (includes 10x for intra-species extrapolation and 10x for inter-species variation).

$$\textbf{Acute RfD} = \frac{\text{250 mg/kg/day NOAEL)}}{\text{100 (UF)}} = \textbf{2.5 mg/kg/day}$$

This risk assessment is required.

A.2. Acute Reference Dose (Acute RfD) General Population including Infants and Children.

An appropriate endpoint attributable to a single exposure was not available from the toxicity studies, including the developmental toxicity studies; the maternal toxicity in these studies are not attributable to a single exposure. Therefore, there is no dose selected for the general population including infants and children

This risk assessment is NOT required for this population (No acute RfD)

B. Chronic RfD

The RfD was established in 1994 by the RfD Committee.

Study Selected: Chronic Feeding - Dog §83-1

MRID No.: 42189501

Executive Summary: A 60-week study was conducted with male and female beagle dogs. Chlorpropham was fed in the diet to give dose levels of 0, 5, 50, 350 or 500 mg/kg/day. The diets containing 350 or 500 mg/kg/day were unpalatable causing marked reductions in food consumption and body weight gain during the initial weeks of the study. Food consumption returned to normal by the dogs adapting to the diet or manipulation of the test material concentration; however, bodyweight gain of the 350 and 500 mg/kg/day dose groups remained depressed throughout the study. Anemia was evident at the two highest dose levels. Erythrocyte count, hemoglobin and hematocrit were reduced, and mean corpuscular volume (MCV) was increased. Changes in thyroid function and morphology were prominent effects of treatment. At 50 mg/kg/day and above thyroid weight was increased and histopathological changes were observed. The thyroid showed moderate to marked changes characterized by irregular

shaped follicles lined by medium to high cuboidal epithelium; follicles contained clear to pale stained colloid. Serum T_3 and T_4 levels were reduced at 350 and 500 mg/kg/day. Thyroid response to TSH was depressed at these dose levels. Cholesterol was increased at 350 and 500 mg/kg/day. The NOAEL was 5 mg/kg/day. The LOAEL was 50 mg/kg/day based on evidence of thyroid effects at this dose level. (MRID 42189501)

Dose and Endpoint for Establishing RfD: NOAEL = 5 mg/kg/day based on thyroid effects at 50 mg/kg/day (LOAEL).

Uncertainty Factor(s): 100 (includes 10x for intra-species extrapolation and 10x for inter-species variation).

$$\textbf{Chronic RfD} = \frac{\text{5 mg/kg/day (NOAEL)}}{\text{100 (UF)}} = \textbf{0.05 mg/kg/day}$$

Comments about Study/Endpoint/Uncertainty Factor(s): The HIARC concurred with the dose, endpoint, uncertainty factor, and the study used in 1994 by the RfD/Peer Review Committee.

This risk assessment is required.

C. Occupational/Residential Exposure

1. Dermal Absorption

Dermal Absorption Factor: No dermal absorption studies are available. The Committee estimated a dermal absorption rate of 50% based on the results of an oral developmental toxicity and a 21-day dermal toxicity study in the same species (rabbits) with similar endpoints (i.e. alterations in hematopoietic system).

In the oral developmental toxicity study in rabbits, the maternal NOAEL was 500 mg/kg/day and the LOAEL was 500 mg/kg/day based on clinical signs of cold ears which are attributable to anemia (MRID 00129940).

In the 21-day dermal toxicity study in rabbits, the systemic toxicity NOAEL was 500 mg/kg/day and the LOAEL was 1000 mg/kg/day based on increased reticulocyte count which may be indicative of a decreased red cell life span and subsequent increase in hemopoiesis (MRID 41899901).

A ratio of the LOAELs from the oral and dermal studies, indicated an approximate dermal absorption rate of 50% (oral LOAEL 500 mg/kg/day / dermal LOAEL of 1000 mg/kg/day x 100 = 50%).

Dermal Absorption Factor: 50% (estimated)

2. Short-Term Dermal (1-7 days)

Study Selected: 21-day Dermal Toxicity Study - Rat §82-2

MRID No.: 41899901

Executive Summary: Groups of male and female New Zealand White rabbits received repeated dermal applications of Chlorproham (96.2%) at dose levels of 0, 100, 500 or 1000 mg/kg/day, 6 hours/day for 21 consecutive days. Dermal irritation consisted of minimal to slight acanthosis, hyperkeratosis, and focal inflammatory infiltrate of the treated skin. There were no treatment-related effects on survival, body weight, organ weight or clinical chemistry. Systemic toxicity was characterized as increases in reticulocyte count (208% and 233% of controls in males and females, respectively $p < 0.01$). The NOAEL was 500 mg/kg/day and the LOAEL was 1000 mg/kg/day based on the increase in reticulocyte counts.

Dose and Endpoint for Risk Assessment: Systemic toxicity = 500 mg/kg/day based on the increase in reticulocyte counts at 1000 mg/kg/day (LOAEL).

Comments about Study/Endpoint:Study Selected: The NOAEL (500 mg/kg/day) in this study is comparable to the dermal equivalent dose derived by using the developmental NOAEL of 250 mg/kg/day established in the developmental rabbit study and the use of a 50% dermal absorption rate ($250 \div 0.5 = 500$ mg/kg/day).

This risk assessment is required.

3. Intermediate-Term Dermal (7 Days to Several Months)

Study Selected: Chronic Feeding - dog §83-1

MRID No.: 42189501

Executive Summary: see Chronic RfD in section II. B.

Dose and Endpoint for Risk Assessment: NOAEL = 5 mg/kg/day based on thyroid effects at 50 mg/kg/day (LOAEL).

Comments about Study/Endpoint: The endpoint selected for this risk assessment is based on the statistically significant decreases in thyroxine (T_4) levels seen at Week 14 in male at 50, 350 or 500 mg/kg/day. T_4 levels were also decreased at this interval but the decreases did not show statistical significance when compared to controls. Additionally, this endpoint is supported by the results of a 28-day feeding study in rats , in which the LOAEL of 50 mg/kg/day was established based on histopathological alterations in the thyroid glands; the NOAEL was 5 mg/kg/day (MRID 41899001). Since an oral NOAEL was selected a dermal absorption rate of 50% should be used for route-to-route extrapolation.

This risk assessment is required.

4. Long-Term Dermal (Several Months to Life-Time)

Study Selected: Chronic Feeding - dog §83-1

Executive Summary: see Chronic RfD in section II. B.

Dose and Endpoint for Risk Assessment:NOAEL = 5 mg/kg/day based on thyroid effects at 50 mg/kg/day (LOAEL).

Comments about Study/Endpoint: This dose/endpoint/study was selected to derived the RfD. Since an oral NOAEL was selected a dermal absorption rate of 50% should be used for route-to-route extrapoaltion.

5. Inhalation Expsoure (Any Time Period)

The Committee selected the oral NOEL of 5 mg/kg/day for inhalation risk assessments for any time period (short, intermediate, or long-term) due to the lack of an inhalation study (study was waived) and because of the concern for potential for exposure via this route from both occupational and residential exposures.

Since the dose identified for inhalation risk assessment is from an oral study (i.e., an oral NOEL was selected), the following steps should be used for route-to-route extrapolation:

Step 1 The inhalation exposure component (i.e. ug a.i/L./day) using 100% absorption rate (default value) and application rate should be converted to an **equivalent oral dose** (mg/kg/day).

Step 2 The Intermediate and Long-Term dermal expsoure component (mg/kg/day) using 50% absorption rate and application rate should be converted to an **equivalent oral**

dose (mg/kg/day). Combine this dose to the converted dose in Step 1.

Step 3 This combined dose should then be compared to the oral NOAEL of 5 mg/kg/day to calculate the MOEs.

NOTE: For Short-Term risk assessment, the dermal exposure should NOT be combined with inhalation expsoure since a dermal NOAEL was used. However, it is appropriate to combine the dermal and inhalation exposure to get the total exposure for Intermediate and Long-Term risk assessments since oral NOAEL was selected for these exposures.

Separate MOEs should be calculated for Short-Term dermal (using the Dermal NOAEL) and Short-Term inhalation exposures.

D. Recommendation for Aggregate Exposure Risk Assessments

For **acute** aggregate exposure risk assessment, combine the high end exposure values from food + water and compare it to the acute RfD.

Aggregate risk assessments for short, intermediate or long-term exposure from dermal and inhalation exposures can NOT be performed since different toxicology endpoints were identified for the oral (developmental toxicity), dermal (hematopoietic), and inhalation (thyroid effects) exposure risk assessments.

E. Margins of Exposures for Occupational/Residential Exposure Risk Assessments

A MOE of 100 is adequate for occupational exposure risk assessments. The MOE for residential exposure will be determined during risk characterization by the FQPA Safety Committee.

III. CLASSIFICATION OF CARCINOGENIC POTENTIAL

1. Carcinogenicity Study in Rats

Executive Summary

In a two year toxicity/carcinogenicity study, chlorpropham (96% a.i.) was administered in the diet to groups of 50 male (104 weeks) and 50 female (101 weeks) Sprague-Dawley rats at dietary levels to provide an intake of 0, 30, 100, 500 or 1000 mg/kg/day. Additional animals (10/sex/group) received the same doses and were sacrificed at 53 weeks.

At 100 mg/kg/day, red blood cell counts (RBC) were decreased about 10% in both sexes at weeks 26 and 53 and hemoglobin (HGB) and hematocrir (HCT) values were slightly but significantly reduced in females. At 12 months, a slight increase in splenic

extra medullary hematopoiesis (erythropoiesis) and hemosiderosis was seen in feamles. Heomsiderosis was increased in severity and incidence at 24 months and marked cellularity in the bone marrow was observed, particularary in the females receiving 100 mg/kg/day, but the effects on the red cell parameters were not seen at 78 weeks or at termination. Serum cholesterol levels were slightly increased (40-50%a0 at weeks 53 and 78 in males receiving 100 mg/kg/day.

In addition, in the two highest dose groups (500 and 100 mg/kg/day), there was an increase in the incidence and/or severity of hematopoiesis in the liver, spleen and bone marrow in both sexes; an increased incidence of hemosiderosis and congestion in the spleen in both sexes; and an increase pigment accumulation in the liver and the kidney tubules of both sexes. Also at the 500 and 1000 mg/kg/day dose levels in both sexes, there was a significant decrease in red blood cell parameters (RBC, HCT and HGB) and an increase in reticulocyte counts at most intervals of analysis as well as urinary bilirubin. A destruction of red blood cells and a compensatory response were clearly apparent in both sexes at ≥100 mg/kg/day. In addition, a decrease in body weight (20-30% lower than controls at 104 weeks; both sexes) and body weight gain (25-40% lower than controls at 104 weeks; both sexes), an increase in food consumption, an increase in serun cholesterol, and an increase in spleen size and weight were also observed at 500 and 1000 mg/kg/day in both sexes. The LEL of 100 mg/kg/day is based on the effects on hematology parameters, hemosiderosis in the spleen, hematopoiesis in the spleen, erythropoiesis in the bone marrow, particularly in females, and increased serum chloesterol in males. The NOEL is 30 mg/kg/day.

Under the conditions of the study, there was a significant increase in benign interstitial cell tumors in the testes of male trats receiving 1000 mg/kg/day (9/60 compared to 1/57 for controls).

MRID No.: 42754701, 43158401

Discussion of Tumor Data The only test material related neoplastic lesion seen with chlorpropham in this study were benign testicular Leydig Cell tumors and focal cell hyperplasia of the testicular Leydig Cells at the highest dose level tested in rats. Male rats had a significant difference in the pair-wise comparison of the 1000 mg/kg/day dose group with the controls, for testicular Leydig Cell benign tumors, both at $p < 0.01$. There was also a significant difference in the pair-wise comparison of the 30 mg/kg/day dose group with the controls for testicular Leydig Cell benign tumors at $p < 0.05$. There were no significant test material related tumors observed in female rats. These statistical analyses were based upon Peto's prevalence test since there was a statistically significant negative trend for mortality in male rats with increasing doses of chlorpropham. The statistical evaluation of mortality indicated a significant decreasing trend with increasing doses of chlorpropham in both male and female rats. Female rats also showed significant differences in the pair-wise comparisons of mortality of the controls with the 30, 500 and 1000 mg/kg/day dose groups. The statistical evaluation of mortality was based upon the Thomas, Breslow and Gart computer program. No Leydig Cell tumors or focal cell hyperplasia were seen in animals from the interim sacrifice and only 1, 1, 0 and 4 tumors were seen in dead or sacrificed moribund

animals at 0, 30, 100, 500 and 1000 mg/kg/day, respectively. Historical control data from a limited number of animals (100) indicated a 4% incidence and an incidence in combined controls and negative dosed groups [Since the testing laboratory had conducted only 2 other carcinogenicity studies with Charles River CD Sprague-Dawley rats, controls and dosed groups where no significant increase in testicular Leydig Cell tumors occurred were combined to increase the number of animals included in the historical control data base. These dosed groups were called "negative dosed groups." Historical control data were submitted by the testing laboratory from 2 studies from Charles River, the animal supplier. The 2 studies from the testing laboratory indicated a testicular Leydig Cell tumor incidence of 16 of 350 animals (4.6%) with a range of 3.0% to 6.7%. Data from Charles River indicated 55 of 880 animals (6.3%, range 0-12%) (Tables 2 and 3). The HDT testicular Leydig Cell tumor incidence is 9 of 40 animals (22%), but the overall testicular Leydig Cell tumor incidence in the controls and dosed groups from the submitted study was 20 of 297 (6.7%).

Adequacy of the Dose Levels Tested The adequacy of the dosing is indicated by the compensated RBC destruction at 100, 500 and 1000 mg/kg/day and the statistically significant lower body weight, the lower body weight gain than in controls and the decreased relative efficiency of food utilization in males and females at the two highest dose levels. The body weight changes in the males and females at 500 mg/kg/day indicate that this dose level is adequate to assess the carcinogenic potential of chlorpropham; the 1000 mg/kg/day dose level was possibly excessive.

2. Carcinogenicity Study in Mice

Executive Summary

Chlorpropham was fed in the diets of CD-1 mice for 18-months at dietary levels to provide a test material intake of about 0, 100, 500 or 1000 mg/kg/day.

NOEL (systemic) = 100 mg/kg/day.

LEL (systemic) = 500 mg/kg/day based on increased hemosiderosis of the spleen and increased hematopoiesis of the spleen, liver, and bone marrow in both sexes in response to destruction or loss of erythrocytes. Dark eyes and bluish extremities were also noted.

In addition, at the highest dose tested (limit dose of 100mg/kg/day) an increase in parent reticulocyte was seen in males at 12 and 18 months and in females at 12 months; this was accompanied by an increase in MCH and MCHC in both sexes. In addition, survival was significantly lower in males receiveing 100 mg/kg/day than in controls. High-dose males had increased speen and liver weight. The tset material was not found to be carcinogenic in this study.

MRID No. 42530301

Discussion of Tumor Data: No dose related tumors were reported. No statistically significant increases in the incidence of neoplasia in any tissue/organ were observed in either sex when compared with concurrent control values. Total tumor count (all tumor types in all organs/tissue, benign and malignant) were nominally increased in females 16 at 1000 mg/kg/day versus 14 in controls, but none were statistically significant. The incidence of all neoplasia were within the normal range for 18-month studies in the Charles River CD-1 (ICR) mice (Data submitted to Clement International Corp.: Lang, P., Charles River Laboratories, 1991 and data submitted to T.P.S. Laboratories from Charles River). This was the first mouse carcinogenicity study conducted at the testing laboratory in the Charles River CD-1 mouse, thus historical control data from the animal supplier were the only data available other than the concurrent control data.

Adequacy of the Dose Levels Tested: Chlorpropham was administered to both sexes of mice at greater than the limit dose level at the highest dose tested. Since no increased tumor incidence occurred over concurrent controls or historical controls at this limit dose level, higher dose levels need not be considered. The dose levels were adequate to assess the carcinogenic potential of chlorpropham in the mouse. The mean chlorpropham consumption over the course of the study at the nominal dose levels of 100, 500 or 1000 mg/kg/day were 108.9 ± 9.2, 523.0 ± 42.0 and 1050.6 ± 82.8 mg/kg/day, respectively. No consistent dose related body weight or body weight gains were observed. Mortality was determined at week 13, 26, 52, 65 and 78. Statistically significant increased mortality occurred in males (58%) at the 1000 mg/kg/day dose level compared with
control values (86%) at week 78. In terminal females at the same dose level, there was a nominal increase in mortality (78% versus 84% in controls). The major cause of death was reported to be amyloidosis. The Charles River CD-1 mouse typically has a high background for amyloidosis.

3. Classification of Carcinogenic Potential

The Cancer Peer Review Committee has classified chlorpropham as a Group E Chemical; no evidence of carcinogenicity, based on the lack of carcinogenic potential in mice or rats (CPR document dated August 22, 1994). The HIARC concurred with this classification.

IV. MUTAGENICITY

Three acceptable studies on chlorpropham were available for review; summaries of these studies follow:

Gene Mutations

1) Mouse lymphoma (L5178Y TK +/-)(MRID 00129938) - Complete toxicity occurred at chlorpropham concentrations of 1000-10,0000 μg/ml with or without metabolic activation (PCB-induced rat liver S9). Concentrations of 13 to 75 μg/ml were tested without metabolic activation; growth was 41 to 100% of control cultures. Concentrations of 13 to 100 μg/ml were tested with metabolic activation; growth was 8

to 52% of control cultures. Chlorpropham had no effect on mutation frequency with or without metabolic activation.

Chromosome Aberrations

2) In vitro chromosome aberrations in CHO cells (MRID 41846201) -Metaphase cells were collected 10 and 20 hours after treatment. Concentrations of 149 μg/ml and higher were toxic. Concentrations tested ranged from 10 to 160 μg/ml with or without metabolic activation (PCB-induced rat liver S9). Chlorpropham was positive with metabolic activation at moderately toxic doses (120 and 140 μg/ml). Chlorpropham was negative without metabolic activation, but this portion was incompletely performed.

Other Mutagenic Mechanisms

3) In vitro cell transformation using Syrian hamster embryo cells (MRID 41845501) - Six concentrations of chlorpropham (5-30 μg/ml) were tested in a continuous (7-day) exposure regimen. Five concentrations (85-115 μg/ml) were tested for 24 hours, which included a 7-day refeeding regimen. Chlorpropham was positive for producing morphological transformations. Both the continuous exposure and the 24 hour exposure resulted in a significant increase in the frequency of transformations.

Other Metabolites

4) Two potential metabolites of chlorpropham were evaluated in the Salmonella typhimurium mutation assay using tester strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538. The compounds tested were isopropyl 5-chloro-2-hydroxycarbanilate and isopropyl 3-chloro-4-hydroxycarbanilate. Both tested negative with and without metabolic activation (PCB-induced rat liver S9) (MRID 00126733, 00126734).

V. FQPA CONSIDERATIONS:

1. Neurotoxicity:

In an acute oral delayed neurotoxicity study (MRID 00093915), groups of 10 domestic hens were dosed with 0 (corn oil control), 1250, 2500 or 5000 mg/kg/day chlorpropham. Ten hens were dosed with 500 mg/kg TOCP as the positive control. No deaths occurred and all hens appeared to be in good health. All TOCP treated hens showed signs of ataxia and one hen was sacrificed on day 15. All control and chlorpropham treated hens showed an increase in body weight in the post-dosing period (21 days). The TOCP treated hens showed a decrease in body weight. Food consumption was variable in all groups. There were no signs of delayed neurotoxicity (ataxia) in chlorpropham treated hens. Histologic lesions were observed in the TOCP treated hens which correlated with the ataxia observed. There were no histologic lesions considered to be treatment related in chlorpropham treated hens.

The study is classified as Core-Minimum Data and it satisfies the requirement for a guideline series 81-7 acute delayed toxicity study.

There are no acute or subchronic neurotoxicity screening batteries in rats that have been submitted to date. The HIARC recommended that the Registrant should conduct an acute neurotoxicity study in rats because of the effects seen in the hematopoietic system in the several studies in the database. This stud (acute neurotoxicity) should include the meausrement of methemoglobinemia (at peak time) along with chloineseterase measurement and histopathology. This study is required for better hazard characterization of chlorpropham.

2. Developmental Toxicity:

Chlorpropham, technical (Lot# 237-2778 BR 21-80, about 98% pure), was administered daily by gavage (corn oil vehicle) to 25 presumed pregnant Sprague Dawley rats per group at 0, 100, 350 or 1000 mg/kg/day from day 6 through 19 of gestation (MRID 00093921). From gestational day 6 to 20 maternal body weight gain was 89% of controls, $p \leq 0.05$, at 350 mg/kg-rat and 83% of controls, $p \leq 0.01$, at 1000 mg/kg-rat. Spleen weights increased 157% of controls at 350 mg/kg-rat and 171% of controls at 1000 mg/kg/day. Possible developmental toxicity was noted at the 1000 mg/kg-rat dose level by an increase in the 14th rudimentary rib (52% vs. 24% in control litters).

Historical control data indicated that in the strain of rat, the incidence of 14th rudimentary rib ranged from 8% to 42.9% in litters. The maternal toxic LOEL = 350 mg/kg/day and the NOEL = 100 mg/kg/day based on body weight gain decrement. The developmental toxic LOAEL = 1000 mg/kg/day and the NOAEL = 350 mg/kg/day based on increased incidence of 14th rudimentary rib.

This study is classified Core-Minimum Data (Acceptable) and satisfies the requirement (83-3) for a developmental toxicity (teratology) study in rats.

In a developmental toxicity study (MRID 00129939), pregnant female Sprague-Dawley COBS CD rats were given multiple daily doses of 40.2% chlorpropham on Hi-Sil 233 by intragastric intubation at dose levels of 0, 0, 40, 400 and 2000 mg/kg/day CIPC. They were dosed during organogenesis (gestation days 6-19) and sacrificed on gestation day 20.

Lethality of dams was observed at 2000 mg/kg/day (3 of 25 died between days 10 and 13). Decreased body weight gain, pale extremities and ears, bloodied facial fur and stained urogenital fur were observed at 2000 mg/kg/day. Pale extremities and ears were also observed at 400 mg/kg/day. Cerebral hemorrhage, darkening and enlargement of the spleen (possibly stressed induced hematopoiesis) and reversible gastrointestinal bleeding and lesion were observed at necropsy in 2000 mg/kg/day dams. Enlarged darkened spleens were also observed at 400 mg/kg/day. A high rate of post-implantation loss due to early resorption was observed at 2000 mg/kg/day. Fetal weights were 20% lower at 2000 mg/kg/day compared to controls and other dosed animals. Skeletal anomalies observed at 2000 mg/kg/day included bent ribs and

limb bones, maligned sternebrae, and reduced ossification of the pubic bones and vertebral arches. The LOAEL for maternal toxicity was 400 mg/kg/day based on pale extremities and ears and enlarged darkened spleens. The NOAEL was 40 mg/kg/day. The LOAEL for developmental effects was 2000 mg/kg/day based on skeletal anomalies and increased early resorption. The NOAEL was 400 mg/kg/day.

The study is classified as Guideline and it satisfies the requirement for a guideline series 83-3a developmental toxicity study.

Chlorpropham, technical (98.5% pure), was administered daily by gavage (Vehicle was 1% methylcellulose in water) to 16 presumed pregnant New Zealand White rabbits per group at 0, 125, 250 or 500 mg/kg/day from day 6 through 18 of gestation MRID 00129940). An increased incidence in the number of animals and number of clinical observations such as cold ears, soiled ano-genital area/blood in urine and reduced fecal output was noted at 500 mg/kg/day. Body weights and body weight gains were comparable with controls in all groups. In a range-finding study at 0, 200, 500, 1500 and 800 mg/kg/day all animals at 1500 and 800 mg/kg/day were killed in a moribund condition. Thus, 500 mg/kg/day was adequate (sufficiently close to a toxic dose level) to determine potential developmental toxicity from chlorpropham exposure. Possible developmental toxicity was noted at the 500 mg/kg-rabbit dose level by an increase resorption and increased post implantation loss. The submitted early and late resorption combined was statistically significant increased (1.8/litter versus 0.7/litter in controls, $p \leq 0.01$) at 500 mg/kg/day and post implantation loss was statistically significantly increased (19.0% versus 7.2% in controls, $p \leq 0.05$) at 500 mg/kg/day. Both of these were higher than the respective mean, but within the historical control range submitted with the study. Early and late embryonic death mean of 1.0/litter, range of 0.0-2.5/litter and post implantation loss mean of 10.8%, range of 0.0-24.7%. The maternal toxic LOAEL = 500 mg/kg/day and the NOAEL = 250 mg/kg/day based on clinical signs of cold ears and reduced fecal output. The developmental toxic LOAEL = 500 mg/kg/day and the NOAEL = 250 mg/kg/day based on increased resorption and post implantation loss.

This study is classified as Core Minimum Data (Acceptable) and satisfies the requirement (§ 83-3) for a developmental toxicity (teratology) study in rabbits.

3. Reproductive Toxicity

In a reproductive toxicity study (MRID 00129545), chlorpropham (98%) was administered in the diet at 0, 1000, 3000 or 10,000 ppm (approximate doses of 0, 50, 150 or 500 mg/kg/day) to male and female Sprague-Dawley rats (15 male, 30 female per group) for 14 weeks prior to dosing and during the mating, gestation and lactation periods (total of 164-165 days). Mating and fertility indices in the F_0 and F_1 rats were not significantly reduced. Similarly, there was no effect on the length of gestation, mean litter size and survival for the F_1 and F_2 pups. There were no compound related abnormalities. Body weight gain was slowed in rats dosed at 3000 and 10,000 ppm, but no effect was seen at 1000 ppm. No compound related gross lesions were seen in any rats, except the culled F_1 adults. They included dose-related histopathologic findings of brown pigment granules in the reticuloendothelial cells of the spleen and

liver and the convoluted tubular epithelial cells of the kidney, and marrow hypercellularity. Rats dosed at 3000 and 10,000 ppm were most affected. Organ weight changes in the F_1 pups (lactation day 21) included mild dose-related decreases in absolute and relative ovary weights in all dosed groups and mild decreases in absolute and organ/brain weight ratios for liver (3000 and 10,000 ppm) and spleen (10,000 ppm). In the F_1 adults, a severe increase in absolute and relative spleen weights was seen in males (10,000 ppm) and females (3000 and 10,000 ppm). The F_2 pups had mild to moderate absolute and relative organ weight decreases for ovaries (3000 and 10,000 ppm) and spleens (10,000 ppm). Measurements of cholinesterase levels in the brain, plasma and erythrocytes of the F_1 rats did not reveal any significant changes. The only compound related effect seen in the 1000 ppm dose group was a mild decrease in mean ovary weights in the F_1 pups. Since no ovarian lesions were observed grossly or microscopically in these pups and the F_1 adults had normal ovarian morphology, the decreased ovarian weights were probably just an indication of slight development delay. The LOAEL for reproductive effects was not determined; the NOAEL $\geq$ 10,000 ppm 500 mg/kg/day). The LOAEL for systemic effects was 3000 ppm (150 mg/kg/day) based on slow weight gain; microscopic lesion in the kidneys, spleen, liver and marrow; gross splenic lesions; organ weight changes in the ovaries, liver and spleen. The systemic NOAEL = 1000 ppm (50 mg/kg/day).

The study is classified as Core-Guideline and it satisfies the requirement for a guideline series 83-4 reproductive toxicity study.

4. Determination of Susceptibility

The data provided no indication of increased susceptibility in rats or rabbits from *in utero* and/or post natal exposure to chlorproham. In the prenatal developmental toxicity study in rats, the NOAEL for developmental toxicity was higher than the maternal NOAEL. In the developmental toxicity study in rabbits, developmental toxicity was seen in the presence of maternal toxicity at the highest dose level. In the two-generation reproduction study in rats, no offspring toxicity was seen even at the highest dose tested.

5. Recommendation for a Developmental Neurotoxicity Study

The Committee determined that, based on a weight-of-the-evidence review of the available data, a developmental neurotoxicity study with chlorpropham in rats was not required.

i. Evidence that suggest requiring a developmental neurotoxicity study:

None

i. Evidence that do not support a need for a developmental neurotoxicity study:

No evidence of neuropathology was seen in the acute and subchronic toxicity studies. Neither brain weight nor histopathology (nonperfused)

of the nervous system were affected by treatment in the subchronic or chronic toxicity studies.

No evidence of functional abnormalities were seen in the rat and rabbit developmental toxicity or the two-generation reproduction studies.

6. Determination of the FQPA Safety Factor:

The application of an FQPA factor for the protection of infants and children from exposure to chlorproham as required by FQPA, will be determined during risk characterization by the FQPA Safety Factor Committee. However, based on hazard assessment alone, the HIARC recommends to the FQPA Safety Factor Committee that the additional 10x factor should be removed because:

(i) The data provided no indication of increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure.

(ii) No evidence of developmental anomalies, including abnormalities in the development of fetal nervous system, was observed in the pre-and/or postnatal studies.

(iii) The toxicology data base is complete and there are no data gaps.

VI. DATA GAPS

None

VII. ACUTE TOXICITY

Acute Toxicity of Chlorpropham

Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
81-1	Acute Oral	41013703 41763601	LD_{50} > 4 g/kg	III
81-2	Acute Dermal	41013704	LD_{50} > 5 g/kg	IV
81-3	Acute Inhalation	waived		
81-4	Primary Eye Irritation	41013705 41763301	mild irritant	III
81-5	Primary Skin Irritation	41013706 41763501	mild irritant	IV
81-6	Dermal Sensitization	41013707 41763401	negative	N/A
81-8	Acute Neurotoxicity	00093915	negative	N/A

VII. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected for various exposure scenarios are summarized below.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary Females 13+	NOAEL = 250 UF = 100	Increased resorption and post-implantation loss	Developmental Toxicity-Rat
	Acute RfD = 2.5 mg/kg		
Acute Dietary General Population including Infants and Children	None	An appropriate endpoint attributable to a single exposure was not available from the database including the developmental toxicity studies; the maternal endpoints are not attributable to single exposure. This risk assessment is NOT required.	
Chronic Dietary	NOAEL = 5 UF = 100	Thyroid effects	Chronic Toxicity - Dog
		Chronic RfD = 0.05 mg/kg/day	
Short-Term (Dermal)	Dermal NOAEL = 500	Statistically significant increase in reticulocyte counts	21-Day Dermal Toxicity Study in rabbits
Intermediate-Term (Dermal)[a]	Oral NOEL = 5	Based on the statistically significant decreases in thyroxine (T_4) levels seen at Week 14	Chronic Toxicity-Dog
Long-Term (Dermal)[a]	Oral NOEL = 5	Thyroid effects	Chronic Toxicity-Dog
Inhalation (Any Time Period) [b]	Oral NOEL = 5	Thyroid effects	Chronic Toxicity - Dog

a = Since an oral NOAEL was selected, a dermal absorption rate of 50% should be used for route-to-route

b = Since an oral NOAEL was selected an inhalation absorption factor (100%) should be used for route-to-route extrapolation.

HED DOC. NO. 013027

17-DEC-1998

MEMORANDUM

SUBJECT: ***CHLORPROPHAM*** - Report of the FQPA Safety Factor Committee.

FROM: Brenda Tarplee, Executive Secretary
FQPA Safety Factor Committee
Health Effects Division (7509C)

THROUGH: Ed Zager, Chair
FQPA Safety Factor Committee
Health Effects Division (7509C)

TO: Steve Knizner, Branch Senior Scientist
Reregistration Branch 3
Health Effects Division (7509C)

PC Code: 018301

The Health Effects Division (HED) FQPA Safety Factor Committee met on December 14, 1998 to evaluate the hazard and exposure data for chlorpropham and recommended that the FQPA Safety Factor (as required by Food Quality Protection Act of August 3, 1996) be removed in assessing the risk posed by this chemical.

I. HAZARD ASSESSMENT

1. Determination of Susceptibility

The Hazard Identification Assessment Review Committee (HIARC) determined that the available Agency Guideline studies indicated no increased susceptibility of rats or rabbits (quantitatively or qualitatively) to *in utero* and/or pre/postnatal exposure to chlorpropham. In the two prenatal developmental toxicity studies in rats, the NOAELs for developmental toxicity were higher than those for maternal toxicity. In the developmental toxicity study in rabbits, developmental toxicity was seen only in the presence of maternal toxicity at the highest dose tested. In the two-generation reproduction study in rats, no offspring toxicity was observed even at the highest dose tested (*Memorandum:* W. Greear to J. Rowland dated October 16, 1998).

2. Adequacy of Toxicity Database

There are **no data gaps** for the assessment of the effects of chlorpropham following *in utero* and/or postnatal exposure. Based on the toxicity profile, a developmental neurotoxicity study in rats is not required.

II. EXPOSURE ASSESSMENT AND RISK CHARACTERIZATION

1. Dietary (Food) Exposure Considerations

Chlorpropham (CIPC) is currently registered for indoor use on potatoes as a sprout growth inhibitor. The postharvest application to stored potatoes is the only food/feed use of chlorpropham that will be supported by the registrants for reregistration.

The HED Metabolism Assessment Review Committee (MARC) concluded that for potatoes, the tolerance expression include only parent, chlorpropham *per se*; and for animal commodities, the tolerance expression include parent and the metabolite 4-hydroxychlorpropham-O-sulfonic acid. Although 3-chloroaniline is not to be included in the tolerance expression(s), the MARC determined that it should be included in the risk assessment (D188707, 7/1/94).

A tolerance reassessment was conducted for the HED Chapter of the Reregistration Eligibility Document (RED) for Chlorpropham (1/26/95), wherein HED concluded that the submitted residue data on stored potatoes indicate that the established tolerance for potatoes may be reduced from 50 ppm to 30 ppm with restricted treatment rates. Additionally, a tolerance of 150 ppm on processed potato waste is required and tolerances (permanent and interim) on poultry commodities and on plants other than potatoes are to be revoked. Tolerances on milk and the meat, fat, and meat byproducts of cattle, goats, hogs, horses, and sheep will be determined when a ruminant feeding study for chlorpropham is submitted.

USDA Pesticide Data Program (PDP) and FDA monitoring data are available for this chemical. PDP data indicate that detectable residues of chlorpropham are found on 60% of potatoes (limit of detection is ≤13 ppb). Percent crop treated (%CT) information are also available.

The HED Dietary Risk Evaluation System (DRES) was used to assess the risk from dietary exposure to chlorpropham residues in food. This analysis included %CT information, the reassessed tolerances for potatoes, as well as interim tolerance levels for milk and meat and results in a somewhat more realistic estimate of dietary exposure. It is noted that potatoes contribute significantly to the diets of the general U.S. population and of children aged 1-6.

2. Dietary (Drinking Water) Exposure Considerations

Chlorpropham is currently registered for indoor use as a plant growth regulator on stored potatoes (postharvest). This postharvest application to stored potatoes is the only food/feed use that will be supported by the registrant. This use is not expected to result in any quantifiable contamination of surface or ground water.

3. Residential Exposure Considerations

There are currently no registered residential uses of chlorpropham therefore, this type of exposure to infants and children is not expected..

III. SAFETY FACTOR RECOMMENDATION AND RATIONALE

1. FQPA Safety Factor Recommendation

The Committee recommended that the **FQPA safety factor** for protection of infants and children (as required by FQPA) be **removed.**

2. Rationale for Removal of the FQPA Safety Factor

The Committee recommended that the FQPA safety factor be removed since: 1) the toxicology data base is complete; 2) there is no indication of increased susceptibility of rats or rabbit fetuses to *in utero* and/or postnatal exposure in the developmental and reproductive toxicity studies; 3) a developmental neurotoxicity study is not required; 4) dietary (food) exposure estimates are partially refined (using reassessed tolerances, % CT, and interim tolerances for milk and meat) resulting in a more realistic estimate of dietary exposure; 5) quantifiable contamination of surface or ground water is not likely to result from this use; and 6) there are currently no registered residential uses of chlorpropham, therefore, this type of exposure to infants and children is not expected.

SignOff Date:	01/1399
DP Barcode:	D207525
HED DOC Number:	013069
Toxicology Branch:	TOX2